What is claimed is:

1. An adzyme for enzymatically altering a substrate, the adzyme comprising: a catalytic domain that catalyzes a chemical reaction converting said substrate to one or more products, and a targeting moiety that reversibly binds with an address site on said substrate or with an address site on a second molecule that occurs in functional proximity to the substrate, wherein

said targeting moiety and said catalytic domain are heterologous with respect to each other,

said targeting moiety, when provided separately, binds to the substrate,

said catalytic domain, when provided separately, catalyzes the chemical reaction converting said substrate to one or more products, and

said adzyme has one or more properties, with respect to the reaction with said substrate, of (a) a potency at least 2 times greater than the catalytic domain or the targeting moiety alone; (b) a k_{on} of 10^3 $M^{-1}s^{-1}$ or greater; (c) a k_{cat} of 0.1 sec^{-1} or greater; (d) a K_D that is at least 5 fold less than the K_m of the catalytic domain; (e) a k_{off} of 10^{-4} sec^{-1} or greater, (f) a catalytic efficiency at least 5 fold greater than the catalytic efficiency of the catalytic domain alone, (g) a K_m at least 5 fold less than the K_m of the catalytic domain alone, and/or (h) an effective substrate concentration that is at least 5 fold greater than the actual substrate concentration.

2. An adzyme for enzymatically altering a substrate, the adzyme comprising: a catalytic domain that catalyzes a chemical reaction converting said substrate to one or more products, and a targeting moiety that reversibly binds with an address site on said substrate or with an address site on a second molecule that occurs in functional proximity to the substrate, wherein

said substrate is an extracellular signaling molecule,

said targeting moiety and said catalytic domain are heterologous with respect to each other,

said targeting moiety, when provided separately, binds to the substrate,

said catalytic domain, when provided separately, catalyzes the chemical reaction converting said substrate to one or more products, and

said adzyme is more potent than said catalytic domain or targeting moiety with respect to the reaction with said substrate.

3. An adzyme for enzymatically altering a substrate, the adzyme comprising a polypeptide comprising: a catalytic domain that catalyzes a chemical reaction converting said substrate to one or more products, a targeting domain that reversibly binds with an address site on said substrate or with an address site on a

second molecule that occurs in functional proximity to the substrate, and a linker joining said catalytic domain and said targeting domain, wherein

said substrate is a receptor,

said targeting moiety and said catalytic domain are heterologous with respect to each other,

said targeting domain, when provided separately, binds to the substrate,

said catalytic domain, when provided separately, catalyzes the chemical reaction converting said substrate to one or more products, and

said adzyme is more potent than said catalytic domain or targeting moiety with respect to the reaction with said substrate.

4. An adzyme for enzymatically altering a substrate, the adzyme comprising: a catalytic domain that catalyzes a chemical reaction converting said substrate to one or more products, and a targeting moiety that reversibly binds with an address site on said substrate or with an address site on a second molecule that occurs in functional proximity to the substrate, wherein one or more of said products is an antagonist of an activity of said substrate.

5. An adzyme for enzymatically altering a substrate, the adzyme comprising: a catalytic domain that cleaves at least one peptide bond of said substrate to produce one or more products, and a polypeptide targeting domain that reversibly binds with an address site on said substrate or with an address site on a second molecule that occurs in functional proximity to the substrate, wherein

said chimeric protein construct is resistant to cleavage by the catalytic domain,

said targeting moiety, when provided separately, binds to the substrate,

said catalytic domain, when provided separately, cleaves at least one peptide bond of said substrate to produce one or more products, and

said adzyme is more potent than said catalytic domain or targeting moiety with respect to the reaction with said substrate.

6. An adzyme for enzymatically altering a substrate, the adzyme comprising a polypeptide comprising: a catalytic domain that catalyzes a chemical reaction converting said substrate to one or more products, a targeting domain that reversibly binds with an address site on said substrate or with an address site on a second molecule that occurs in functional proximity to the substrate, and a linker joining said catalytic domain and said targeting domain, wherein

said substrate is an extracellular polypeptide signaling molecule,

said targeting moiety and said catalytic domain are heterologous with respect to each other,

said targeting domain, when provided separately, binds to said substrate,

said catalytic domain, when provided separately, catalyzes the chemical reaction converting said substrate to one or more products, and

said adzyme is more potent than said catalytic domain or targeting moiety with respect to the reaction with said substrate.

7. The adzyme of claim 1, wherein the substrate is endogenous to a human patient.

8. The adzyme of claim 7, wherein the effect of the adzyme on the substrate is effective against the target molecule in the presence of physiological levels of an abundant human serum protein.

9. The adzyme of claim 8, wherein the abundant human serum protein is human serum albumin.

10. The adzyme of claim 2, wherein said adzyme has one or more properties, with respect to the reaction with said substrate, of (a) a potency at least 2 times greater than the catalytic domain or the targeting moiety alone; (b) a k_{on} of 10^3 $M^{-1}s^{-1}$ or greater; (c) a k_{cat} of 0.1 sec^{-1} or greater; (d) a K_D that is at least 5 fold less than the K_m of the catalytic domain; (e) a k_{off} of 10^{-4} sec^{-1} or greater, (f) a catalytic efficiency at least 5 fold greater than the catalytic efficiency of the catalytic domain alone, (g) a K_m at least 5 fold less than the K_m of the catalytic domain alone, and/or (h) an effective substrate concentration that is at least 5 fold greater than the actual substrate concentration.

11. The adzyme of claim 10, wherein the potency of the adzyme is at least 5 times greater than the catalytic domain or the targeting moiety alone.

12. The adzyme of claim 10, wherein the k_{on} is 10^6 $M^{-1}s^{-1}$ or greater.

13. The adzyme of claim 10, wherein the k_{cat} is 10 sec^{-1} or greater.

14. The adzyme of claim 10, wherein the K_D is at least 50 fold lower than the K_m of the catalytic domain.

15. The adzyme of claim 10, wherein the k_{off} is 10^{-3} s^{-1} or greater.

16. The adzyme of claim 10, wherein the catalytic efficiency is at least 20 fold greater than that of the catalytic domain alone.

17. The adzyme of claim 10, wherein the K_m is at least 20 fold less than that of the catalytic domain alone.

18. The adzyme of claim 1, wherein the potency of the adzyme is at least 5 times greater than the catalytic domain or the targeting moiety alone.

19. The adzyme of claim 1, wherein the k_{on} is $10^6 M^{-1}s^{-1}$ or greater.

20. The adzyme of claim 1, wherein the k_{cat} is 10 sec^{-1} or greater.

21. The adzyme of claim 1, wherein the K_D is at least 50 fold lower than the K_m of the catalytic domain.

22. The adzyme of claim 1, wherein the k_{off} is 10^{-3} s^{-1} or greater..

23. The adzyme of claim 1, wherein the catalytic efficiency is at least 20 fold greater than that of the catalytic domain alone.

24. The adzyme of claim 1, wherein the K_m is at least 20 fold less than that of the catalytic domain alone.

25. The adzyme of claim 1, wherein said adzyme is a fusion protein.

26. The adzyme of claim 25, wherein said fusion protein includes a linker between said catalytic domain and said targeting moiety.

27. The adzyme of claim 25, wherein said linker is an unstructured peptide.

28. The adzyme of claim 3, wherein said linker is an unstructured peptide.

29. The adzyme of claim 27, wherein said linker includes one or more repeats of Ser_4Gly or $SerGly_4$.

30. The adzyme of claim 3, wherein said linker includes one or more repeats of Ser_4Gly or $SerGly_4$.

31. The adzyme of claim 25, wherein said linker is selected to provide steric geometry between said catalytic domain and said targeting moiety such that said adzyme is more potent than said catalytic domain or targeting moiety with respect to the reaction with said substrate.

32. The adzyme of claim 3, wherein said linker is selected to provide steric geometry between said catalytic domain and said targeting moiety such that said adzyme is more potent than said catalytic domain or targeting moiety with respect to the reaction with said substrate.

33. The adzyme of claim 25, wherein said linker is selected to provide steric geometry between said catalytic domain and said targeting moiety such that said address moiety presents the substrate to the enzymatic domain at an effective concentration at least 5 fold greater than would be present in the absence of the address moiety.

34. The adzyme of claim 3, wherein said linker is selected to provide steric geometry between said catalytic domain and said targeting moiety such that said address moiety presents the substrate to the enzymatic domain at an effective concentration at least 5 fold greater than would be present in the absence of the address moiety.

35. The adzyme of claim 25, wherein the fusion protein is a cotranslational fusion protein encoded by a recombinant nucleic acid.

36. The adzyme of claim 3, wherein the fusion protein is a cotranslational fusion protein encoded by a recombinant nucleic acid.

37. The adzyme of claim 1, wherein the substrate is a biomolecule produced by a cell.

38. The adzyme of claim 1, wherein said substrate is a polypeptide.

39. The adzyme of claim 1, wherein the substrate is a polysacccaride, a nucleic acid, a lipid, or a small molecule.

40. The adzyme of claim 1, wherein the substrate is a diffusible extracellular molecule.

41. The adzyme of claim 40, wherein the diffusible extracellular molecule is an extracellular signaling molecule.

42. The adzyme of claim 41, wherein the extracellular signaling molecule is an extracellular polypeptide signaling molecule.

43. The adzyme of claim 40, wherein the extracellular signaling molecule is selected from among: interleukin-1 and TNF-alpha.

44. The adzyme of claim 41, wherein the extracellular signaling molecule binds to a cell surface receptor and triggers receptor-mediated cellular signaling.

45. The adzyme of claim 1, wherein said substrate is a receptor.

46. The adzyme of claim 45, wherein said substrate is a unique receptor subunit of a heteromeric receptor complex.

47. The adzyme of claim 37, wherein the biomolecule is a component of a biomolecular accretion.

48. The adzyme of claim 47, wherein the biomolecular accretion is selected from among: an amyloid deposit and an atherosclerotic plaque.

49. The adzyme of claim 37, wherein the biomolecule is a biomolecule produced by a pathogen.

50. The adzyme of claim 49, wherein the pathogen is selected from among, a protozoan, a fungus, a bacterium and a virus.

51. The adzyme of claim 37, wherein the biomolecule is a prion protein.

52. The adzyme of claim 1, wherein said substrate comprises a polypeptide and wherein said catalytic domain is a protease that cleaves at least one peptide bond of the substrate.

53. The adzyme of claim 52, wherein said adzyme is resistant to cleavage by said catalytic domain.

54. The adzyme of claim 3, wherein said catalytic domain is a protease that cleaves at least one peptide bond of the substrate.

55. The adzyme of claim 54, wherein said adzyme is resistant to cleavage by said catalytic domain.

56. The adzyme of claim 52, wherein said protease is a zymogen.

57. The adzyme of claim 54, wherein said protease is a zymogen.

58. The adzyme of claim 52, wherein said adzyme is purified from a cell culture in the presence of a reversible protease inhibitor.

59. The adzyme of claim 54, wherein said adzyme is purified from a cell culture in the presence of a reversible protease inhibitor.

60. The adzyme of claim 1, wherein said catalytic domain modifies one or more pendant groups of said substrate.

61. The adzyme of claim 1, wherein said substrate includes a chiral atom, and said catalytic domain alters the ratio of stereoisomers.

62. The adzyme of claim 38, wherein said catalytic domain alters the level of post-translational modification of the polypeptide substrate.

63. The adzyme of claim 6, wherein said catalytic domain alters the level of post-translational modification of the polypeptide substrate.

64. The adzyme of claim 62, wherein the post-translation modification is selected from the group consisting of glycosylation, phosphorylation, sulfation, fatty acid modification, alkylation, prenylation and acylation.

65. The adzyme of claim 63, wherein the post-translation modification is selected from the group consisting of glycosylation, phosphorylation, sulfation, fatty acid modification, alkylation, prenylation and acylation.

66. The adzyme of claim 1, wherein the catalytic domain is selected from the group consisting of: a protease, an esterase, an amidase, a lactamase, a cellulase, an

oxidase, an oxidoreductase, a reductase, a transferase, a hydrolase, an isomerase, a ligase, a lipase, a phospholipase, a phosphatase, a kinase, a sulfatase, a lysozyme, a glycosidase, a nuclease, an aldolase, a ketolase, a lyase, a cyclase, a reverse transcriptase, a hyaluronidase, an amylase, a cerebrosidase and a chitinase.

67. The adzyme of claim 3, wherein the catalytic domain is selected from the group consisting of: a protease, an oxidase, an oxidoreductase, a reductase, a transferase, a hydrolase, an isomerase, a lipase, a phospholipase, a phosphatase, a kinase, a sulfatase, a glycosidase, an aldolase, a ketolase, a lyase, a cyclase, a hyaluronidase, and a cerebrosidase.

68. The adzyme of claim 1, wherein the adzyme is resistant to autocatalysis.

69. The adzyme of claim 68, wherein the adzyme is resistant to autocatalysis at an adzyme concentration that is about equal to the concentration of adzyme in a solution to be administered to a subject.

70. The adzyme of claim 37, wherein said adzyme alters the half-life of the biomolecule in vivo.

71. The adzyme of claim 2, wherein said adzyme alters the half-life of the substrate in vivo.

72. The adzyme of claim 37, wherein said adzyme alters the distribution of the biomolecule in vivo.

73. The adzyme of claim 2, wherein said adzyme alters the distribution of the substrate in vivo.

74. The adzyme of claim 37, wherein said adzyme reduces a biological activity of said biomolecule.

75. The adzyme of claim 2, wherein said adzyme reduces a biological activity of said substrate.

76. The adzyme of claim 37, wherein said biomolecule binds a plurality of different molecules in vivo, and said adzyme alters the binding specificity of said biomolecule.

77. The adzyme of claim 2, wherein said substrate binds a plurality of different molecules in vivo, and said adzyme alters the binding specificity of said substrate.

78. The adzyme of claim 37, wherein said adzyme alters the interaction of said biomolecule with other molecules in vivo.

79. The adzyme of claim 2, wherein said adzyme alters the interaction of said substrate with other molecules in vivo.

80. The adzyme of claim 78, which alters one or more of: a receptor-ligand interaction, a protein-protein interaction and a DNA-protein interaction.

81. The adzyme of claim 79, which alters one or more of: a receptor-ligand interaction, a protein-protein interaction and a DNA-protein interaction.

82. The adzyme of claim 37, which reduces receptor-mediated or ion channel-mediated signal transduction.

83. The adzyme of claim 3, which reduces receptor-mediated or ion channel-mediated signal transduction.

84. The adzyme of claim 37, which alters proliferation, differentiation or viability of a cell in vivo or in vitro.

85. The adzyme of claim 2, which alters proliferation, differentiation or viability of a cell in vivo or in vitro.

86. The adzyme of claim 1, wherein said product of said chemical reaction is an antagonist of said substrate.

87. The adzyme of claim 1, wherein said product of said chemical reaction has an increased biological activity relative to said substrate.

88. The adzyme of claim 37, which alters an intrinsic enzymatic activity of said biomolecule.

89. The adzyme of claim 2, which alters an intrinsic enzymatic activity of said substrate.

90. The adzyme of claim 1, wherein said substrate is a polypeptide.

91. The adzyme of claim 90., wherein said polypeptide is present in biological fluid of an animal.

92. The adzyme of claim 6, wherein said extracellular polypeptide signaling molecule is present in biological fluid of an animal.

93. The adzyme of claim 91, wherein said biological fluid is blood or lymph.

94. The adzyme of claim 92, wherein said biological fluid is blood or lymph.

95. The adzyme of claim 90, wherein said polypeptide substrate is a polypeptide hormone, a growth factor and/or a cytokine.

96. The adzyme of claim 92, wherein said extracellular polypeptide signaling molecule is a polypeptide hormone, a growth factor and/or a cytokine.

97. The adzyme of claim 91, wherein said polypeptide is selected from the group consisting of four-helix bundle factors, EGF-like factors, insulin-like factors, β-trefoil factors and cysteine knot factors.

98. The adzyme of claim 92, wherein said extracellular polypeptide signaling molecule is selected from the group consisting of four-helix bundle factors, EGF-like factors, insulin-like factors, β-trefoil factors and cysteine knot factors.

99. The adzyme of claim 91, wherein said polypeptide is a pro-inflammation mediator and said enzyme construct reduces the pro-inflammatory activity of said polypeptide factor.

100. The adzyme of claim 92, wherein said extracellular polypeptide signaling molecule is a pro-inflammation mediator and said enzyme construct reduces the pro-inflammatory activity of said polypeptide factor.

101. The adzyme of claim 91, wherein said polypeptide is Interleukin-1 or TNFα, and said adzyme reduces the activity of the substrate in vivo.

102. The adzyme of claim 92, wherein said extracellular polypeptide signaling molecule is Interleukin-1 or TNFα, and said adzyme reduces the activity of the substrate in vivo.

103. The adzyme of claim 1, wherein the substrate is an intracellular biomolecule.

104. The adzyme of claim 103, wherein said adzyme further comprises a transcytosis moiety that promotes transcytosis of the adzyme into the cell.

104. The adzyme of claim 1, wherein the targeting moiety comprises a polypeptide or polypeptide complex.

105. The adzyme of claim 1, wherein said targeting moiety is a polyanionic or polycatonic binding agent.

106. The adzyme of claim 1, wherein said targeting moiety is an oligonucleotides, a polysaccharide or a lectin

107. The adzyme of claim 1, wherein the targeting moiety is an antibody or polypeptide(s) including an antigen binding site thereof.

108. The adzyme of claim 107, wherein the targeting moiety is selected from the group consisting of a monoclonal antibody, an Fab and $F(ab)_2$, an scFv, a heavy chain variable region and a light chain variable region.

109. The adzyme of claim 1, wherein said substrate is receptor ligand, and said targeting moiety includes a ligand binding domain of a cognate receptor of said ligand.

110. The adzyme of claim 1, wherein said targeting moiety is an artificial protein or peptide sequence engineered to bind to said substrate.

111. The adzyme of claim 1, wherein said substrate is a receptor, and said targeting moiety is a cognate ligand of said receptor.

112. The adzyme of claim 3, wherein said targeting moiety is a cognate ligand of said receptor.

113. The adzyme of claim 101, wherein the substrate is TNFα and wherein the targeting moiety binds to TNFα.

114. The adzyme of claim 102, wherein the substrate is TNFα and wherein the targeting moiety binds to TNFα.

115. The adzyme of claim 113, wherein the catalytic domain comprises a protease that decreases TNFα pro-apoptotic activity.

116. The adzyme of claim 114, wherein the catalytic domain comprises a protease that decreases TNFα pro-apoptotic activity.

117. The adzyme of claim 115, wherein the protease is selected from among: MT1-MMP; MMP12; tryptase; MT2-MMP; elastase; MMP7; chymotrypsin; and trypsin.

118. The adzyme of claim 116, wherein the protease is selected from among: MT1-MMP; MMP12; tryptase; MT2-MMP; elastase; MMP7; chymotrypsin; and trypsin.

119. The adzyme of claim 113, wherein the targeting moiety is selected from among, a soluble portion of a TNFα receptor and a single chain antibody that binds to TNFα.

120. The adzyme of claim 114, wherein the targeting moiety is selected from among, a soluble portion of a TNFα receptor and a single chain antibody that binds to TNFα.

121. The adzyme of claim 113, wherein the targeting moiety is an sp55 portion of TNFR1.

122. The adzyme of claim 114, wherein the targeting moiety is an sp55 portion of TNFR1.

123. The adzyme of claim 101, wherein the substrate is IL-1 and wherein the targeting moiety binds to IL-1.

124. The adzyme of claim 102, wherein the substrate is IL-1 and wherein the targeting moiety binds to IL-1.

125. The adzyme of claim 123, wherein the catalytic domain comprises a protease that decreases an IL-1 bioactivity.

126. The adzyme of claim 124, wherein the catalytic domain comprises a protease that decreases an IL-1 bioactivity.

127. An adzyme preparation for therapeutic use in a human patient, the preparation comprising an adzyme of claim 1.

128. The adzyme preparation of claim 127, further comprising a pharmaceutically effective carrier.

129. The adzyme preparation of claim 127, wherein the adzyme preparation is formulated such that autocatalytic modification of the adzyme is inhibited.

130. The adzyme preparation of claim 129, wherein the adzyme comprises a catalytic domain that is a protease.

131. The adzyme preparation of claim 130, further comprising a reversible inhibitor of said protease.

132. The adzyme preparation of claim 131, wherein the reversible inhibitor is safe for administration to a human patient.

133. The adzyme preparation of claim 127, wherein said adzyme preparation is substantially pyrogen free.

134. The adzyme preparation of claim 127, wherein said adzyme preparation is packaged with instructions for administration to a patient.

135. A method of making a medicament for use in treating a disorder that is associated with an activity of the substrate of an adzyme of claim 1, the method comprising formulating the adzyme for administration to a human patient.

136. A method of making a medicament for use in treating an inflammatory or allergic disorder, the method comprising formulating an adzyme of claim 1 for administration to a human patient in need thereof, wherein the substrate of the adzyme is an inflammatory cytokine.

137. A method of treating a disorder that is associated with an activity of the substrate of an adzyme of claim 1, the method comprising administering a therapeutically effective dose of the adzyme to a human patient in need thereof.

138. A method of treating an inflammatory of allergic disorder, the method comprising administering a therapeutically effective dose of an adzyme to a human patient in need thereof, wherein the substrate of the adzyme is an inflammatory cytokine.

139. A nucleic acid comprising a coding sequence for the adzyme of claim 3.

140. A nucleic acid encoding a coding sequence for the adzyme of claim 25.

141. An expression vector comprising the nucleic acid of claim 139, wherein the expression vector directs expression of the adzyme in a suitable host cell.

142. An expression vector comprising the nucleic acid of claim 140, wherein the expression vector directs expression of the adzyme in a suitable host cell.

143. A cell comprising the expression vector of claim 141.

144. A cell comprising the expression vector of claim 142.

145. A cell comprising a first nucleic acid comprising a first coding sequence and a second nucleic acid comprising a second coding sequence, wherein the first coding sequence encodes a first fusion protein comprising an immunoglobulin heavy chain and a catalytic domain, and wherein the second coding sequence encodes a second fusion protein comprising an immunoglobulin heavy chain and a targeting domain.

146. The cell of claim 145, wherein, in appropriate culture conditions, the cell secretes an adzyme comprising an Fc fusion protein construct that is a dimer of the first fusion protein and the second fusion protein.

147. A method for manufacturing an adzyme, the method comprising
a) culturing a cell of claim 143 in conditions that cause the cell to produce the adzyme encoded by the expression vector; and
b) purifying the adzyme to substantial purity.

148. A method for manufacturing an adzyme, the method comprising
a) culturing a cell of claim 144 in conditions that cause the cell to produce the adzyme encoded by the expression vector; and
b) purifying the adzyme to substantial purity.

149. A method for manufacturing an adzyme, the method comprising
a) culturing a cell of claim 146 in conditions that cause the cell to produce the adzyme; and
b) purifying the adzyme to substantial purity.

150. The method of claim 147, wherein the purifying the adzyme to substantial purity includes the use of a reversible inhibitor that inhibits autocatalytic activity of the catalytic domain.

151. The method of claim 147, wherein the catalytic domain of the adzyme is a protease domain, and wherein purifying the adzyme to substantial purity includes the use of a reversible protease inhibitor that inhibits the protease activity of the catalytic domain.

152. A method of designing and constructing an effective adzyme, the method comprising:
a) selecting a substrate that is a known target for a therapeutically effective binding agent;
b) testing a plurality of catalytic domains for effectiveness in reducing an activity of the substrate to obtain a set of one or more candidate catalytic domains that are effective in reducing an activity of the substrate;
c) testing a plurality of binding moieties for effectiveness in binding to the substrate to obtain a set of one or more candidate targeting moieties that are effective in binding to the substrate;
d) constructing and producing a plurality of adzymes comprising one or more of the candidate catalytic domains and one or more of the candidate targeting moieties, wherein the one or more catalytic domains and the one or more candidate targeting moieties are associated in at least two different geometric conformations,

e) testing the plurality of adzymes for effectiveness in reducing an activity of the substrate to obtain a set of one or more candidate adzymes, wherein an adzyme that is effective for reducing an activity of the substrate is an effective adzyme.

153. The method of claim 152, further comprising testing the efficacy of the adzyme in an organism.

154. The method of claim 152, further comprising modifying an effective adzyme to improve one or more of the following properties:
a) reduce the amount of autocatalysis;
b) increase the potency of the adzyme;
c) increase the specificity of the adzyme;
d) improve the balance of the potency and specificity of the adzyme;
e) increase the serum half-life of the adzyme;
f) decrease the interactions between the adzyme and one or more abundant serum proteins.

155. A method of operating a therapeutic adzyme business, the method comprising:
a) designing an adzyme according to the method of claim 152;
b) testing the adzyme for safety and effectiveness in humans;
c) arranging for distribution and marketing of the adzyme.